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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
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| 09/966,803 | 09/27/2001 | Jay Short | DIVER1130-8 | 3294 |

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| EXAMINER | |
|---|---|
| RAMIREZ, DELIA M | |

| ART UNIT | PAPER NUMBER |
|---|---|
| 1652 | |

DATE MAILED: 04/21/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 09/966,803 | SHORT ET AL. | |
| | Examiner | Art Unit | |
| | Delia M. Ramirez | 1652 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *28 January 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *42-55 and 93-107* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *55,72,93-104,106 and 107* is/are rejected.

7)☒ Claim(s) *105* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *2/17/2004* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

## DETAILED ACTION

### *Status of the Application*

Claims 42-55 and 93-107 are pending.

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 1/28/2005 has been entered.

Applicant's amendment of claims 42-43, 55, 93, 99-101, 106, addition of claim 107, and submission of a declaration under 37 CFR 1.132 by inventor Jay Short, in a communication filed on 1/28/2005 are acknowledged.

Claims 42-55 and 93-107 are under consideration and are being examined herein.

Rejections and/or objections not reiterated from previous office actions are hereby withdrawn.

### *Specification*

1. The disclosure is objected to because it lacks a paper copy of the sequence listing. See 37 CFR 1.821-1.825 and MPEP §§ 2421-2431. Appropriate correction is required.

### *Claim Objections*

2. Claims 93 and 106 is objected to due to the recitation of "template sequence" and "template polynucleotide". It appears from what is recited in the claims that the term "template" is not further limiting the terms "sequence" or "polynucleotide". Thus, for clarity and consistency, it is suggested that the term "template" be removed. For examination purposes, the terms will be interpreted as "sequence" and "polynucleotide". Appropriate correction is required.

***Claim Rejections - 35 USC § 112, Second Paragraph***

3. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

4. Claims 42-55, 93-104, 106 remain rejected and new claim 107 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. This rejection is necessitated by amendment.

5. Claims 42, 93, 100, 106 (claims 43-55, 94-99, 101-104 and 107 dependent thereon) are indefinite in the recitation of "activity equivalent to the amidase activity of a polypeptide having a sequence as set forth in SEQ ID NO: 2" as it is unclear absent a statement defining what is encompassed by the term "equivalent", or the basis to determine equivalence in regard to amidase activity. For example, one cannot determine if the equivalence is in regard to substrates, level of activity in the presence of a particular substrate at specific conditions, etc. For examination purposes, it will be assumed that the term reads "the same amidase activity as that of the polypeptide of SEQ ID NO: 2". Correction is required.

6. Claims 94-98 are indefinite in the recitation of "wherein the nucleic acid comprises at least X consecutive nucleotides" for the following reasons. As written, one cannot determine if the recited limitation refers to (a) the number of consecutive nucleotides of the polynucleotide having at least 90% sequence identity to the polynucleotide of SEQ ID NO: 1, or (b) the total number of nucleotides in the nucleic acid modified in the method. For examination purposes, it will be assumed that the term reads "wherein the nucleic acid comprises at least X consecutive nucleotides of a polynucleotide having at least 90% sequence identity to the polynucleotide of SEQ ID NO: 1" . Correction is required.

7. Claim 100 (claim 101 dependent thereon) is indefinite in the recitation of "at least about" for the following reasons. The use of this language is contradictory because the term "about" can be interpreted

as "less than" whereas the term "at least" is synonym of "no less than". For examination purposes, it will be assumed that the term reads "at least". Correction is required.

8. Claim 102 is indefinite in the recitation of "at least 80% sequence identity" since the recited limitation does not further limit claim 42 as it encompasses a broader genus than that of claim 42, from which claim 102 depends. For examination purposes, it will be assumed that claim 102 is a duplicate of claim 42. Correction is required.

9. Claim 103 (claim 104 dependent thereon) is indefinite in the recitation of "at least 90% sequence identity" since the recited limitation does not further limit claim 42 as it encompasses the exact same genus of claim 42, from which claim 103 depends. For examination purposes, it will be assumed that claims 42 and 103 are duplicates. Also, it will be assumed that claim 104 depends upon claim 42. Correction is required.

10. Claim 106 is indefinite in the recitation of "template sequence" as there is no antecedent basis for a "template sequence". For examination purposes, it will be assumed the term reads "template polynucleotide". Correction is required.

***Claim Rejections - 35 USC § 112, First Paragraph***

11. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

12. Claims 93-99 remain rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

13. This rejection has been discussed at length in the Non Final Action mailed on 5/14/2004.

14. Applicants argue that describing a genus of polynucleotides in terms of physico-chemical properties and function meets the requirement for written description defined in the Written Description Guidelines. Applicants also refer to the USPTO guidelines concerning the written description requirement set forth in 35 USC 112, first paragraph and submit that the genus of polynucleotides recited in the claims are described by function and structure as shown in Example 14 of the guidelines. It is Applicant's contention that the functions of the recited enzymes are sufficiently correlated to a particular, known structure and a physical property. Thus, according to Applicants, the amended claims encompass subject matter which is sufficiently described in the specification.

15. Applicant's arguments have been fully considered but are not deemed persuasive to overcome the instant rejection. The Examiner acknowledges the amendments to the claims; however, the Examiner disagrees with Applicant's contention that the claimed method uses a genus of nucleic acids which is adequately described. First, it is noted that claims 93-99 are directed to a method which requires a genus of polynucleotides encoding polypeptides of any function. Claims 93-99, as interpreted, are directed to a method which requires a genus of nucleic acids of any function, wherein said nucleic acids have at least 30-150 consecutive nucleotides of a polynucleotide encoding a polypeptide having the same amidase activity as that of the polypeptide of SEQ ID NO: 2, wherein said polynucleotide has at least 90% sequence identity to the polynucleotide of SEQ ID NO: 1. See Claim Rejections under 35 USC 112, second paragraph for claim interpretation. It is noted that the recited functional limitation corresponds to the polynucleotide from which the 30-150 consecutive nucleotides are obtained, i.e. polynucleotide having at least 90% sequence identity to the polynucleotide of SEQ ID NO: 1, and does not necessarily apply to the nucleic acid which is being modified in the method.

As indicated previously, and reiterated herein, even if a functional limitation is added to claim 93 (from which claims 94-99 depend), the structural limitations recited, i.e. 30-150 consecutive nucleotides of a polynucleotide having at least 90% sequence identity to the polynucleotide of SEQ ID NO: 1, do not

constitute a substantial portion of the genus as the remainder of any nucleic acid comprising said structural elements is completely undefined, and the specification does not define the remaining structural features for members of the genus to be selected. Thus, contrary to Applicant's assertions , the instant case is not analogous to that described in Example 14 of the guidelines, and the recited genus of nucleic acids is not sufficiently correlated to a particular, known structure and a physical property, such that one of skill in the art can reasonably conclude that the claimed invention is adequately described by the teachings of the specification.

16. Claims 42-55, 93-103, 106 remain rejected and new claim 107 is rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of generating a variant nucleic acid by modifying one or more nucleotides of the polynucleotide of SEQ ID NO: 1, does not reasonably provide enablement for a method of generating a variant nucleic acid by modifying one or more nucleotides of (1) a polynucleotide having at least 90% sequence identity to the polynucleotide of SEQ ID NO: 1 wherein said polynucleotide (a) encodes an amidase capable of catalyzing the hydrolysis of an amine group in the substrates recited, or (b) encodes a polypeptide having the same amidase activity as that of the polypeptide of SEQ ID NO: 2, (2) a polynucleotide comprising at least 30-150 consecutive nucleotides of a polynucleotide having at least 90% sequence identity to the polynucleotide of SEQ ID NO: 1, wherein the polynucleotide encodes a polypeptide having the same amidase activity as that of the polypeptide of SEQ ID NO: 2, or (3) a polynucleotide which hybridizes under the low stringency conditions recited to the polynucleotide of SEQ ID NO: 1, wherein the polynucleotide (a) encodes a polypeptide having the same amidase activity of the polypeptide of SEQ ID NO: 2, or (b) encodes an amidase capable of catalyzing the hydrolysis of an amine group in the substrates recited. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

17. This rejection as it relates to claims 42-55, 93-103, 106 has been discussed at length in the Non Final action mailed on 5/14/2004. This rejection as it relates to claim 107 is necessitated by amendment.

18. Applicants argue that the claims have been amended such that the claimed method only requires nucleic acids having at least 90% sequence identity to the polynucleotide of SEQ ID NO: 1, wherein the nucleic acids encode polypeptides having amidase activity. Applicants submit that the Examiner has not met her initial burden to establish a reasonable basis to question the enablement provided. In particular, Applicants submit that neither Bork, Van de Loo et al., Broun et al., Witkowski et al. or Seffernick et al. discuss whether or not screening a large number of nucleic acid variants would have constituted undue experimentation to one of skill in the art at the time of the invention. Furthermore, Applicants submit that the instant references appear to support the argument that most changes in an enzyme's amino acid sequence are not important in determining or changing its catalytic specificity. Therefore, Applicants submit that these references support the idea that most changes in an enzyme's amino acid sequence will result in little or no effect on its specificity or activity. Applicants also submit that the Examiner did not sufficiently consider Dr. Short's declaration and that the arguments and statements made by Dr. Short are sufficient to rebut any possible prima facie case of lack of enablement. Applicants assert that in Dr. Short's declaration, he states that it would have not been necessary for one of skill in the art to understand which specific regions or structural elements of an amidase were required for function or activity to routinely generate the genus of claimed amidase-encoding nucleic acids. According to Dr. Short, enzyme screening technology, such as high throughput screening, makes methods which require previous knowledge of protein structure obsolete and unnecessary. Applicants also argue that the specification in paragraph 48 provides guidance as to which amino acid substitutions can be made to make the genus of amidase-encoding nucleic acids of the invention. In addition, Applicants submit that the art, as evidenced by Chebrou et al., Novo et al., and Tata et al., provide directions as to which amino acid residues can be substituted, deleted or inserted in a polypeptide to obtain functional homologs of an amidase.

19. Applicant's arguments have been fully considered but are not deemed persuasive to overcome the instant rejection. The Examiner acknowledges the amendments to the claims, Dr. Short's declaration, the teachings of Chebrou et al., Novo et al., and Tata et al., and the teachings of the specification. However the Examiner disagrees with Applicant's contention that the claimed invention is enabled by the teachings of the specification. It is noted that not all claims require a genus of nucleic acids having at least 90% sequence identity to the polynucleotide of SEQ ID NO: 1, and encoding polypeptides (1) having the same amidase activity of the polypeptide of SEQ ID NO: 2, or (2) having the ability to catalyze the hydrolysis of an amine group in the recited substrates, as asserted by Applicants. As previously indicated, claims 93-99 are directed to a method which requires a genus of polynucleotides encoding polypeptides of any function. Claim 106, as interpreted, is directed to a method which requires a genus of nucleic acids wherein said nucleic acids hybridize under low stringency conditions to the polynucleotide of SEQ ID NO: 1, wherein said nucleic acids either encode a polypeptide having the same amidase activity as that of the polypeptide of SEQ ID NO: 2, or encode an amidase capable of catalyzing the hydrolysis of an amine group in the recited substrates.

In regard to the references by Bork, Van de Loo et al., Broun et al., Witkowski et al. and Seffernick et al, it is noted that the instant references were introduced in support of the argument that even in cases where the structural homology is high, functional annotation is unpredictable absent some knowledge or guidance as to how structure correlates with function. It is reiterated herein that testing the extremely large number of variants encompassed by the claims constitutes undue experimentation when there is no guidance as to how structure correlates with function. While the argument can be made that one of skill in the art could predict which variants are most likely to encode polypeptides having amidase activity based on structural homology, thus reducing the number of species to test, the instant references, particularly Broun et al., Witkowski et al., and Seffernick et al., show that even in cases where the species in a genus are extremely similar in structure, one cannot assume functional homology.

In addition, while it is agreed that one of skill in the art would certainly expect changes in the catalytic site of an enzyme to have an effect on activity and/or specificity, it is noted that neither one of these references teach that any amino acid change in the non-catalytic sites would not have any effect on specificity or activity. In fact, one of skill in the art would not expect any amino acid change in the non-catalytic sites to have no effect whatsoever in an enzyme since it is well known in the art that amino acid changes in non-catalytic sites may result in changes in the 3D structure of a protein such that folding would change to the extent that enzymatic activity/specificity is affected. Furthermore, while the catalytic site of an enzyme is essential for enzymatic activity, it is noted that those amino acids which are not part of the catalytic site must have a function associated to an enzyme's activity and/or substrate specificity. This is evidenced by the fact that there is diversity in substrate and/or activity within a family of enzymes.

The Examiner respectfully disagrees with the notion that Dr. Short's declaration has not been sufficiently considered or that such declaration is sufficient to rebut any possible prima facie case of lack of enablement. As previously indicated, while the Examiner agrees that an amidase activity assay is well known in the art, and one could make the numerous species encompassed by the claims using well known molecular biology techniques, producing variants useful as amidases requires that one of skill in the art know or be provided with guidance for the selection of which of the infinite number of variants have the activity. Without such guidance, one of skill in the art would be reduced to the necessity of producing and testing all of the virtually infinite possibilities. Guo et al.(PNAS 101(25):9205-9210, 2004) teach that the percentage of random single substitution mutations which inactivate a protein for the protein 3-methyladenine DNA glycosylase is 34% and that this number appears to be consistent with other studies in other proteins as well. Guo et al. further show in Table 1 that the percentage of active mutants for multiple mutants appears to be exponentially related to this by the simple formula $(.66)^x$ X 100% where x is the number of mutations introduced. Applying this estimate to the instant 90% sequence identity allows up to 62 mutations within the 622 amino acids of SEQ ID NO:2 and thus only $(.66)^{62}$ X 100% or

6.48 x $10^{-10}$% of random mutants having 90% sequence identity would be active, whereas at 95% sequence identity 2.5 x $10^{-4}$% of random mutants would be active. Therefore, to find a single active mutant within random mutants having 90% sequence identity, one of skill in the art would have to screen over a billion mutants (1/6.48 x $10^{-10}$%). While current techniques(i.e., high throughput mutagenesis and screening techniques), in the art would allow for finding a few active mutants within several hundred thousand inactive mutants, finding a few mutants within several billion or more as in the claims to 90% sequence identity would not be possible. Therefore, while enablement is not precluded by the necessity for routine screening, if a large amount of screening is required, as is the case herein, the specification must provide a reasonable amount of guidance with respect to the direction in which the experimentation should proceed so that a reasonable number of species can be selected for testing. In view of the fact that such guidance has **not** been provided in the instant specification, it would require undue experimentation to enable the full scope of the claims.

In regard to the teachings of the specification or those of the art cited by Applicants, it is noted that contrary to Applicant's assertion, nowhere in the specification, including the section specified by applicants, one could find a teaching or suggestion as to which amino acids in the polypeptide of SEQ ID NO: 2 can be modified and obtain homologs having the same amidase activity as that of the polypeptide of SEQ ID NO: 2. The section of the specification indicated by applicants merely defines what constitutes a conservative substitution, and a substantially identical amino acid sequence, and presents a statement indicating that polypeptides having amidase activity may have certain amino acids removed and still have the same activity, as well as a statement indicating that one could test these modified polypeptides for amidase activity by a number of methods. Similarly, neither the teachings of Chebrou et al., Novo et al., or Tata et al. disclose which amino acids in the polypeptide of SEQ ID NO: 2 can be modified to create the recited homologs and (1) still display the same amidase activity as that of the polypeptide of SEQ ID NO: 2, or (2) have the ability to catalyze the hydrolysis of an amine group in the

recited substrates. Furthermore, none of these references teach the motifs or structural elements required in a polypeptide encoded by the recited nucleic acids such that they would (1) have the same amidase activity as that of the polypeptide of SEQ ID NO: 2, or (2) have the ability to catalyze the hydrolysis of an amine group in the substrates recited. Chebrou et al. discusses a conserved motif found among 21 amidases involved in the reduction of organic nitrogen compounds and ammonia production and suggests that this motif may be important in amide binding. Tata et al. teaches that two specific amino acids are thought to be implicated in the binding of urea and acetamide to the active site of an amidase from Pseudomonas aeruginosa. Novo et al. suggests that a Pseudomonas aeruginosa amidase is related to the nitrilase/cyanide hydratase family and discloses the active site nucleophile for the P. aeruginosa amidase. There is no teaching indicating that the amidase activity displayed by the polypeptide of SEQ ID NO: 2 is the same as that of the Pseudomonas aeruginosa amidase of Tata et al. or Novo et al. Thus, in view of the information provided, the lack of relevant examples, the lack of knowledge regarding the structural elements associated with the required function, and the unpredictability of the art in regard to accurate annotation of function based solely on structural homology, one of skill in the art cannot reasonably conclude that the specification enables the full scope of the claimed invention.

### *Allowable Subject Matter*

20. Claims 104-105 appear to be allowable over the prior art of record but are objected to since they depend upon a rejected base claim.

### *Conclusion*

21. No claim is in condition for allowance.

22. Certain papers related to this application may be submitted to Art Unit 1652 by facsimile transmission. The FAX number is (571) 273-8300. The faxing of such papers must conform with the

notices published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 CFR 1.6(d)). NOTE: If Applicant submits a paper by FAX, the original copy should be retained by Applicant or Applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED, so as to avoid the processing of duplicate papers in the Office.

23. Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PMR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

24. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Delia M. Ramirez whose telephone number is (571) 272-0938. The examiner can normally be reached on Monday-Friday from 8:30 AM to 5:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dr. Ponnathapura Achutamurthy can be reached on (571) 272-0928. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (571) 272-1600.

Delia M. Ramirez, Ph.D.
Patent Examiner
Art Unit 1652

DR
April 15, 2005

REBECCA E. PROUTY
PRIMARY EXAMINER
GROUP ~~1800~~ 1600